II. Formalities

The examiner has requested a substitute specification. Included with this response is a substitute specification which applicants' representative certifies that no new matter is included therein. Also, the examiner has indicated that claims 29 and 48 are substantial duplicates. Applicants traverse, but in the interest of advancing the prosecution, have amend claim 28 to recite inhibition of viral entry and canceled claim 48.

III. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 46 and 47 are rejected under 35 U.S.C. §112, first paragraph, as lacking an enabling disclosure. In short, the examiner doubts the therapeutic efficacy of the approach outlined in the claimed methods. Before going into the specifics of the rejection, applicants seek to clarify the claimed invention as it appears that the examiner may be equating the present invention with a vaccine intended to elicit an immune response. Such is not the case, as discussed below.

The present invention is directed at the use of particular gp120-derived peptides to block the infection of cells by HIV-1. This embodiment is described, for example, at page 14 of the original specification:

> As used herein, the term "HIV infection-inhibiting sequence" refers to a peptide sequence which prevents entry of the HIV virus into its target cell. As such, an inhibitory

peptide may be characterized as including a peptide sequence that is involved in the infection process, or that functions to contact the target cell. Infection-inhibiting peptides particularly include peptides that comprise a sequence wherein antibodies against that sequence are capable of inhibiting HIV cellular infection.

The present invention discloses that synthetic peptides with sequences derived from the HIV-1 *env* gene product, gp120, have the capacity to inhibit HIV cellular infection. In particular, the inventors have identified HIV infection-inhibiting sequences within the V3 loop and at the N-terminal regions of gp120. It is also contemplated that HIV infection-inhibiting sequences may prove to be located within the CD4 binding region.

Thus, it should be clear that the present invention does not rely on the immune system in order to effect blocking of viral infection. Applicants therefor contest the examiner "interpreting [of] the claims to read on a method of vaccinating a subject against HIV infection." Though not believed necessary, in order to more clearly point out and distinctly claim the invention, applicants have amended the main claim to recite direct blocking of virus entry, which excludes the recruitment of immune functions.

Turning to the specific grounds for rejection, applicants note that the examiner points to several problems in the field of HIV therapy that, allegedly, preclude one from accepting the claims on their face: (1) HIV genomic diversity, particularly with respect to envelope proteins; (2) cell to cell passage of virus in "covert" forms or via "virus-free" transmission; (3) latency; (4) "hiding" in the central nervous system; and (5) the complexity and elaboration of the disease. The examiner goes on to state that art accepted animal models can be used to validate the

treatments. Finally, the examiner discusses the attributes and problems with respect to immune therapies and HIV. Applicants seek to address each of these concerns below.

First, dealing with the last point, induction of immunity is absolutely irrelevant to the claimed invention. As indicated quite clearly in the amended claims, the effect of the provided peptide is to directly block virus entry into the host cell. This does not involve any branch of the immune system and, thus, concerns as to the induction of cellular or humoral responses, and their respective abilities to affect HIV infection, are beside the point. Example 8 of the present invention shows remarkable decrease (73.8%) in infection when cells are treated in culture with a peptide according to the present invention. Clearly, there is no effect from immune function needed to achieve this result since it occurred *in vitro*.

Moving on to the other issues, it would appear to reduce to, essentially, two concerns. One basic concern is that the virus will somehow physically evade the effects of a therapeutic agent, for example, by remaining hidden inside cells in a latent state or in a covert form, through virus-free or direct cell-to-cell transmission, or by taking refuge in CNS cells. The other concern is that the virus will genetically evade the therapeutic agent, for example, by mutating its

genome.[1] However, neither of these concerns gives rise to a significant enablement issue for the present claims, as explained below.

Again, applicants refer to the amended claim language which specifically recites the provision of a certain peptide to a cell, whereby the peptide directly blocks the entry of HIV into the cell. The concerns stated above, even if taken as true, would not preclude the present invention from being practiced effectively by the skilled artisan. For example, it is well known that, despite the alternative modes for viral transmission, free infectious virus is found in HIV patients and that this virus infects healthy target cells. See, for example, Wei *et al.*, *Nature* **373**:117-122 (1995); Ho *et al.*, *Nature* **373**:123-126 (1995); Perelson *et al.*, **271**:1582-86 (1996). The ability of the claimed peptides to inhibit infection of cells by HIV has not been effectively challenged. Also, it is important to remember that applicants do not claim a cure for HIV but, rather, a method of inhibiting the progression of the disease by virtue of blocking ***one*** of the modes of virus transmission. It is ***this*** invention that is at issue, not one of disease cure by immunologic means.

While it is true that HIV does undergo remarkable changes in its structure in a human subject, and that many of these changes are found in the gp120 *env* product. The V3 loop

[1] The other stated concern, that the disease is complex and variable, seems to be more a statement of fact than a particular reason why this very specific claim would not be enabled. Such general observations fail to highlight any perceived defect in the claims.

sequences of the present claims represent a common sequence motif from that region of gp120, however, and despite (i) the fact that not all HIV strains will have this sequence, and (ii) the fact that a given virus ***may*** mutate to lose this sequence, there remain a large number of AIDS victims that are infected by a virus having precisely the V3 loop sequences set forth in the claims. Thus, for these patients, the present invention will prove effective at limiting the extent of (not preventing all) viral infection.

This phenomenon further is elucidated in the attached manuscript by Nehete *et al.* This paper describes studies which confirm the present invention by demonstrating the ability of V3 loop peptides to inhibit infection. Interestingly, these V3 loop peptides bind to target cells and are competed with by viral particles, ***but not*** recombinant gp120, sCD4, β-chemokines or antibody to CXCR-4. This difference in competition correlates well with the fact that while many other candidate molecules ***cannot*** effectively inhibit infection, V3 loop peptides can.

The examiner concludes by reference to the Federal Circuit's decision in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). In reviewing the relevant *Wands* factors, each of the various factors which are said to cause undue experimentation are directed to the use of ***vaccines*** and ***immunity***, both of which have been shown to be irrelevant to the present invention. The only other *Wands* factor, relative skill in the art, argues in favor of only routine experimentation.

Thus, it is respectfully submitted that those of skill in the art would find the present invention ***as claimed*** believable and supported by the instant application. Reconsideration and withdrawal of the rejection is respectfully requested.

IV. Rejections Over Haynes *et al.*

Claims 29-45 and 48 are rejected, as not novel or obvious, over Haynes *et al.* The examiner has characterized Haynes as teaching the immunization of animals with peptides "comprising" the claimed amino acid sequences. The method of Haynes *et al.*, while not stated to inhibit HIV infection, is said to produce antiserum that inhibits syncytia formation. Thus, the present claims are believed anticipated or obviated by the reference. Applicants respectfully traverse.

At the outset, applicants note that the examiner alleges that the claims are being examined for their *in vitro* aspects. First, it is respectfully submitted that the examiner has no authority to unilaterally restrict the subject matter ***within a single claim*** that is under examination. If the examiner believes that the claimed subject matter makes an election of species requirement appropriate, then applicants should be afforded the opportunity to determine which embodiment is to be examined first.

Second, it cannot be the case that the examiner is, in fact, examining an *in vitro* embodiment, however. The Haynes *et al.* reference cited against the present claims deals with induction of an immune response against peptides. "Haynes *et al.* teach methods of immunizing animals including mammals .... It would have been obvious ... that the peptides would generate immune responses which would inhibit syncytia formation." Thus, if the present claims truly were being examined with respect to an *in vitro* embodiment, the teachings of Haynes *et al.*, with regard to immunization, would be irrelevant. Applicants can only conclude that the examiner is interpreting the claims, for the purpose of the art rejections, as encompassing *in vivo* methods.

Turning to the present invention, applicants again stress that the claims recite provision of a certain peptide to a cell, whereby the peptide directly blocks the entry of HIV into the cell. It is clear that the prior art is completely silent on this issue. Reference to the Haynes *et al.* specification reveals nothing about non-immune blocking functions for any of these peptides. Rather, Haynes *et al.* teaches immune effects, namely, the production of antibodies against certain peptides, that are able to cross react and in some cases neutralize HIV.

In order for the examiner to make out a *prima facie* case, the following requirements must be met. First, it is necessary that the prior art provide a motivation to make changes to the prior art so as to arrive at the present invention. Second, the enabling technology needed to make

those changes must be available. And third, there must be a reasonable likelihood of success in practicing the present invention. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988). Here, it might be conceded that the technology was available to make any given peptide of 8 to 24 residues and contact that peptide with a cell *in vitro* or *in vivo*. However, indicated above, there clearly was no motivation to provide the claimed peptides to a cell as a direct blocking agent given that the ***only*** known effect for these peptides was to stimulate B-cell or T-cell responses. And most importantly, there was no likelihood of success for the claimed peptides to directly inhibit the infection of cells by HIV. With at best only one of the three *O'Farrell* prongs satisfied, the rejection will not lie.

To highlight the absence of a likelihood of success, applicants direct the examiner to De Rossi *et al.* (1991). In this publication, it was reported that synthetic peptides of 24 amino acid residues from the V3 loop regions of different HIV-1 isolates actually ***enhanced*** the infection of cells by HIV-1 through a CD4-dependent mechanism. Given this showing, there clearly was doubt, in the mind of the skilled artisan, as to the ability of V3 loop peptides to inhibit infection of cells by HIV.

It also is worth mentioning that the examiner's reading Haynes *et al.* data is inappropriate. The examiner notes that serum induced against certain V3 loop peptides can

inhibit syncytia formation. As stated above, the present invention does not rely upon the induction of humoral (or cellular) immune response. More particularly, the examiner's extrapolation from inhibition of syncytia formation to inhibition of infection is not warranted. Several papers indicate that syncytia formation and infection are distinct functions. Camerini and Seed, *Cell* **60**:747-754 (1990); Healey *et al.*, *J. Exp. Med.* **172**:1233-1242 (1990); Lifson *et al.*, 7:449-455 (1991).

In sum, the examiner has misapplied the cited art to the present invention, given the distinctions (immune *versus* non-immune blocking of infection) therebetween. Also, there is a clear indication in the pre-filing literature that one of skill in the art would have doubted the ability of the present invention to achieve the stated goal, namely, direct inhibition of HIV infection. Thus, applicants respectfully request reconsideration and withdrawal of the rejection.

V. Rejections Over Takahashi *et al.*

Claims 29-33, 41 and 48 are rejected, as not novel or obvious, over Takahashi *et al.* The reference is said to teach that the peptides of the instant claims contain epitopes for cytotoxic T cells and, hence, immunization with the peptides would result in "CTL responses ... being effective in inhibiting HIV infection." Applicants again respectfully traverse.

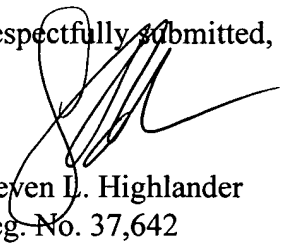
The issues presented by this rejection are almost identical to those discussed above with respect to the Haynes *et al.* reference, the only exception being that the immunization here would allegedly be directed to stimulation of cellular, not humoral, immune responses. Again, it is emphasized that the present invention is directed to a totally distinct embodiment where the provision the peptide ***alone*** is responsible for blocking on viral infection. This is quite distinct from the endeavor of eliciting an immune response, especially a cellular immune response, which could only serve to kill infected cells, and might actually result in ***infection*** of additional cells.

In sum, the concerns raised above regarding a complete lack of motivation for providing peptides as a direct blocking agent, and the teaching away in the art, preclude the assertion of a reasonable *prima facie* case. Therefore, applicants respectfully request reconsideration and withdrawal of this rejection as well.

VI. Conclusion

In light of the foregoing amendments and remarks, applicants respectfully submit that all claims are in condition for allowance and an early indication to that effect is earnestly solicited. Should Examiner Smith have any questions regarding this response, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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